

Pharmacology summary

Nonprescription remedies for treatment of heartburn & dyspepsia.

Neutralization of acids (antacids): Given 1 hour **after a meal** effectively neutralizes gastric acid for up to 2 hours.

Aluminum Hydroxide , Magnesium Hydroxide , Calcium carbonate , Sodium bicarbonate

- React slowly and without gas formation.
- Metabolic alkalosis is also uncommon.
- Mg salts cause diarrhea.
- Aluminum salts cause constipation.
- Usually given in combination.
- Contraindicated in renal insufficiency.
- Aluminum antacids cause constipation, interfere with absorption of many drugs.
- Magnesium antacids have laxative action; diarrhea.
- ionic magnesium stimulates gastric release (acid rebound)
- Magnesium trisilicate slow-acting antacid
- Combination of Magnesium & aluminum antacids are most commonly used (No diarrhea or constipation).

associated with "acid rebound" with excessive chronic use, it may cause milk-alkali syndrome with elevation of serum calcium, phosphate, urea, nitrogen, creatinin & bicarbonate levels.

$$2\text{HCl} + \text{CaCO}_3 \rightarrow \text{CaCl}_2 + \text{CO}_2 + \text{H}_2\text{O}$$

-Should be avoided as it counteracts diuretic therapy for hypertension.

-Short duration of action, followed by acid rebound.

-Highly absorbed, potentially causing metabolic alkalosis.

- CO₂ results in belching.

$$\text{NaHCO}_3 + \text{HCl} \rightarrow \text{NaCl} + \text{H}_2\text{O} + \text{CO}_2$$

H2- Receptor Antagonists

- Cimetidine, prototype, many problems.
- Ranitidine.
- Famotidine.
- 50% first-pass metabolism bioavailability
- Nizatidine
- has little first-pass metabolism
- Decrease secretion stimulated by:
 - Histamine.
 - Gastrin.
 - Acetylcholine.
- Duration of action: 12 hours.
- Inhibit 60-70% of total 24-h acid secretion.
 - 90% of nocturnal acid.
 - 60% of day-time, meal stimulated, acid.

Nocturnal acid is the presence of intragastric pH < 4 during the overnight period for at least 60 continuous minutes

- Clinical Uses:
 - Gastroesophageal Reflux:
 - Prophylactically, before meals.
 - Afford healing for erosive esophagitis in less than 50% of patients.
 - Proton pump inhibitors are preferred.
 - Non Ulcer Dyspepsia.
 - Stress- Related Gastritis:
 - Can prevent bleeding, usually given IV.

Esophagitis is an inflammation of the lining of the esophagus

• Peptic Ulcer Disease:

- Replaced by PPI.
- Healing rate greater than 80-90% after 6-8 weeks.
- Not effective in the presence of H. pylori infection.
- Not effective if NSAID is continued.

Adverse Effects:

- Extremely safe drugs, but can (in 3% of patients) cause diarrhea, headache, fatigue, myalgia and constipation.
- CNS:
 - Confusion, hallucinations occur only with IV cimetidine to elderly patients in ICU.
- Endocrine Effects:
 - Again only with cimetidine, can inhibit estradiol metabolism, and can increase prolactin serum levels.
- Adverse Effects:
 - Pregnancy and Nursing Mothers:
 - Can cross placental barrier and appear in breast milk.
 - Other Effects:
 - Rarely can cause bradycardia and hypotension.

Drug Interactions:

- Cimetidine can inhibit cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2D6, and CYP3A4), so can increase half life of many drugs.
- Ranitidine binds 4-10 times less.
- Nizatidine and famotidine binding is negligible.

Proton Pump Inhibitors, PPI :

- Very efficacious and safe drugs.
- Omeprazole (oral).
- Rabeprazole (oral).
- Lanzoprazole (oral and IV).
- Pantoprazole (oral and IV).
- Esmoprazole (oral and IV).
- Formulated as a prodrug which is released in the intestine.
- Immediate Release Suspension results in rapid response.

Pharmacokinetics:

- They are lipophilic weak bases (pKa 4-5).
- After intestinal absorption, they diffuse across lipid membranes into acidified compartments such as the parietal cell canaliculus.
- The prodrug becomes protonated and concentrated more than 1000-fold within the parietal cells.
- There, it undergoes a molecular conversion to the active form which covalently binds the H⁺/K⁺ ATPase enzyme and inactivates it.

Rabeprazole has immediate release omeprazole have faster onsets of action.

- Should be given one hour before meal.
- Have short half lives but effect lasts for 24 hours due to irreversible inhibition. (covalent binding)

Pharmacodynamics:

- Inhibit both fasting and meal-stimulated secretion because they block the final common pathway of acid secretion (90-98% of 24-hour secretion).

Clinical Uses:

- Gastroesophageal Reflux (GERD):
 - They are the most effective agents in all forms of GERD and complications.
- Nonulcer Dyspepsia:
 - Modest activity.
 - 10-20% more beneficial than a placebo.
- Stress- Related Gastritis:
 - Oral immediate- release omeprazole administered by nasogastric tube.
 - For patients without a nasoenteric tube, IV H₂-antagonists are preferred because of their proven efficacy.
- Gastrinoma and other Hypersecretory Conditions:
 - Usually high doses of omeprazole are used.

- Peptic Ulcer Disease:
 - They heal more than 90% of cases within 4-6 weeks.
 - H.pylori - associated ulcers:
 - PPI eradicate H.pylori by direct antimicrobial activity and by lowering MIC of the antibiotics.
 - Triple Therapy :
 - PPI twice daily.
 - Clarithromycin 500mg twice daily.
 - Amoxicillin 1gm twice daily ,OR, Metronidazole 500mg twice daily.
- Peptic Ulcer Disease:
 - NSAID-associated ulcers:
 - PPIs promote ulcer healing despite continued NSAID use.
 - Also used to prevent ulcer complications of NSAIDs.
 - Rebleeding peptic ulcer:
 - Oral or IV.
 - High pH may enhance coagulation and platelet aggregation.

PPI

Adverse Effects:

General:

- Diarrhea, headache, abdominal pain, not teratogenic in animals, but not used in pregnancy.

Reduction of cyanocobalamine absorption.
Increased risk of GI and pulmonary infection.

Vitamin B12 can help balance immune responses to better fight viral and bacterial infections

Increased serum gastrin levels:

Hyperplasia of ECL cells.

Carcinoid tumors in rats.

Increase proliferative rate of colonic mucosa.

Chronic inflammation in gastric body.

Atrophic gastritis and intestinal metaplasia.

Gastritis is a general term for a group of conditions with one thing in common: Inflammation of the lining of the stomach.

Drug Interactions:

- May affect absorption of drugs due to decreased gastric acidity like digoxin and ketoconazole.
- Omeprazole can inhibit metabolism of drugs such as diazepam and phenytoin.
- Rabeprazole and pantoprazole have no significant interaction.

Laxatives:

Nonpharmacologic Remedies:

- High fiber diet.
- Adequate fluid intake.
- Regular exercise.
- Responding to nature's call.

Bulk-Forming Laxatives:

- Are indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis.
- Can cause bloating and flatus.

Natural Plant Products:

- Psyllium.
- Sterculia "Normacol"
- Methylcellulose.

Synthetic Fibers:

- Polycarbophil.

Stool Surfactant Agents(Softeners):

- They permit water and lipids to penetrate.
 - Given orally or rectally.
 - Docusate.
 - Glycerin suppository.
 - Mineral oil:
 - Clear viscous oil that lubricates fecal material, retarding water absorption from the stool.
 - Used to prevent and treat fecal impaction.
 - Aspiration can cause lipid pneumonia.
 - Can impair absorption of fat-soluble vitamins.
- Aspiration pneumonia occurs when food or liquid is breathed into the airways or lungs, instead of being swallowed.

Osmotic Laxatives(Purgatives):

- Soluble nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.
- Magnesium oxide (Milk of Magnesia):
 - Can cause hypermagnesemia.
 - Large doses of magnesium citrate and sodium phosphate can cause Purgation: rapid bowel evacuation within 1-3 hours. This might cause volume depletion.
- Sorbitol.
- Lactulose.
 - Sugars metabolized by bacteria producing severe flatus and cramps.
- Balanced Polyethylene Glycol:
 - Safe solution: no intravascular fluid or electrolyte shifts. Does not cause cramps or flatus.
 - Used for complete colonic cleansing before endoscopy.
 - PEG is an inert, nonabsorbable, osmotically active sugar.
 - Sodium sulfate, chloride, bicarbonate and potassium chloride.
 - For colonic cleansing, it should be ingested rapidly(4L over 2-4hs).
 - For chronic constipation, PEG powder is mixed with water or juice.

Stimulant Laxatives(Cathartics):

- Direct stimulation of the enteric system.
 - Colonic electrolyte and fluid secretion.
 - Can lead to dependence and destruction of the myenteric plexus resulting in colonic atony and dilation.
 - May be needed in neurologically impaired patients and in bed-bound patients in long term care facilities.
- ## Anthraquinone Derivatives:
- Aloe.
 - Senna.
 - Cascara.
 - Poorly absorbed .
 - After hydrolysis, produce bowel movement in (6-12) hours.
 - Cause brown pigmentation of the colon" Melanosis Coli"
 - Not carcinogenic.
- ## Castor Oil:
- Hydrolyzed in upper intestine into ricinoleic acid which is a local irritant.
 - Was used as purgative to clean the colon before procedures.

Normal situation

- 1-Gut distention stimulates 5-HT release from EC cells.
- 2-Stimulation of 5-HT₃ receptors on the extrinsic afferent nerves, stimulate nausea, vomiting, or abdominal pain.
- 3- 5-HT also stimulates 5-HT_{1P} receptors of the intrinsic primary afferent nerves (IPANs) which activate the enteric neurons responsible for peristaltic and secretory reflex activity.
- 4- Stimulation of 5-HT₄ receptors (5-HT_{4R}) on presynaptic terminals of IPANs enhances release of ACh & calcitonin gene related peptide (CGRP), promoting reflex activity.

Tegaseroid:

- Is a serotonin 5-HT₄ partial agonist, which are presynaptic receptors of the submucosal intrinsic primary afferent nerves which enhance the release of their neurotransmitters.
- These neurones stimulate proximal bowel contraction(via ACh and substance P) and distal relaxation(via nitric oxide and VIP).
- The drug promotes gastric emptying and small and large bowel transit but has no effect on esophageal motility.
- Also stimulates cAMP-dependent chloride secretion leading to increased stool liquidity.

Clinical Uses:

- Chronic constipation.
- Nonulcer dyspepsia.
- Gastroparesis.
- Irritable bowel syndrome.

Adverse Effects:

- Extremely safe drug.
- Diarrhea occurs in 9% of patients but resolves within days.
- Expensive.